## IB. STATUS OF THE CLAIMS

1. (Previously presented) A gene-targeted mouse comprising a modified endogenous apolipoprotein E (apoE) allele, wherein said modified allele comprises an apoE-encoding nucleic acid under transcriptional control of endogenous regulatory sequences, wherein the modified allele encodes a modified apoE polypeptide that exhibits domain interaction characteristic of human apolipoprotein E4 (apoE4), wherein the modified apoE polypeptide comprises a Thr → Arg substitution at a position equivalent to amino acid 61 of human apoE4, and wherein the modified apoE polypeptide exhibits preferential binding to lower density lipoproteins.

2. (Canceled)

3. (Previously presented) The gene-targeted mouse of claim 1, wherein the gene-targeted mouse is homozygous for the modified apoE allele.

4. (Canceled)

5. (Previously presented) A cell isolated from the gene-targeted mouse of claim 1, wherein said cell produces the modified apoE polypeptide.

6. (Canceled)

7. (Previously presented) The cell of claim 5, wherein the cell is homozygous for the modified apoE allele.

8. (Canceled)

9. (Withdrawn) An isolated nucleic acid molecule comprising a nucleotide sequence derived from a non-human apolipoprotein E (apoE) gene, which nucleotide sequence is modified such that it encodes a protein comprising a Thr → Arg substitution at a position equivalent to amino acid 61 of

human apoE4.

10. (Withdrawn) A recombinant vector comprising the nucleic acid of claim 9.

11. (Withdrawn) A recombinant host cell comprising the vector of claim 10.

12. (Withdrawn) A recombinant apolipoprotein E (apoE) protein encoded by a nucleic acid comprising a nucleotide sequence derived from a non-human apoE gene, which nucleotide sequence is modified such that it encodes a protein that exhibits domain interaction characteristic of human apolipoprotein E4 (apoE4).

13. (Withdrawn) The recombinant protein of claim 12, wherein the recombinant protein comprises a Thr → Arg substitution at a position equivalent to amino acid 61 of human apoE4.

14. (Previously presented) A method of identifying an agent that reduces a phenomenon associated with Alzheimer's disease (AD), the method comprising:

a) contacting the gene-targeted mouse of claim 1 with a test agent; and

b) determining the effect of the test agent on reducing a phenomenon associated with AD.

15. (Previously presented) The method of claim 14, wherein the phenomenon associated with AD is selected from the group consisting of amyloid deposits, neuronal cell loss, and neurofibrillary tangles.

16. (Withdrawn) A method for identifying an agent that reduces apolipoprotein E4 domain interaction, the method comprising:

a) contacting the recombinant protein of claim 12 with a test agent; and

b) determining the effect of the test agent on domain interaction.

17. (Withdrawn) The method of claim 16, wherein said determining comprises determining binding of the recombinant apoE to tau.

18. (Withdrawn) The method of claim 16, wherein said determining comprises determining the effect of the agent on binding to VLDL.

19. (Withdrawn) A method of identifying an agent that reduces the risk of heart disease, comprising:

a) contacting the non-human animal of claim 1 with a test agent; and

b) determining the effect, if any, on apoE activity.

20. (Previously presented) The cell according to claim 5, wherein said cell is an astrocyte.

21. (Previously presented) The cell according to claim 5, wherein said cell is a microglial cell.

22. (Previously presented) The cell according to claim 5, wherein the cell is a neuronal cell.